

REMARKS

Claims 1, 9-12, 15 and 16 are pending in the instant application. Claims 1, 9-12, 15 and 16 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Further, Claims 1, 9-12, 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Streetman, D.S., et al. in view of Cook et al., WO2001/96895. The claims have been amended. Applicants respectfully submit that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

Claim 1 has been amended such that:

Step b) includes calculating the metabolic ratios between the probe compounds and their metabolites. Basis for this is found page 16, last paragraph and pages 26 and 30.

Step d) includes grouping individuals according to their metabolic ratios. Basis for this amendment is found in the last paragraph of page 16.

Claims 10 and 16 have been corrected to refer to “more than one probe”.

Claim 15 has been corrected to depend upon claim 1.

Claim rejections – 35 USC 103

Claims 1, 9-12, 15 and 16 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Streetman, D.S., et al. in view of Cook et al., WO2001/96895. This rejection is respectfully traversed.

WO 01/968954 is directed to methods for studying the fate of a test compound in a biological system. It discloses a method for investigating the state of several biological systems wherein NMR active nuclei in samples that are collected from said biological systems which were subjected to a test compound are hyperpolarised. The hyperpolarised

samples are analyzed by NMR spectroscopy and thereby the NMR pattern of the biological systems are determined and compared and it is determined whether the biological systems are in the same or in different states.

WO2001/096895 discloses the following uses:

- Quality assurance testing of systems that are intended to be the same, e.g. cell cultures (page 14, last paragraph)
- Investigating responses of a biological system to a compound about which relatively little is known (page 16, 1st paragraph)
- Studying plants (page 16, 2nd paragraph)

Although WO2001/096895 points out that it is essential to investigate whether trial drugs and their metabolites can give rise to adverse reactions during pre-clinical tests and clinical trial phases (page 2, lines 5-20) there is no suggestion by WO2001/096895 that the testing of such compounds by hyperpolarized NMR can be used for selecting volunteer patients with a specific phenotype and using said volunteer patients in a clinical trial.

Streetman, D.S., et al discloses an evaluation of urinary midazolam MR as an index of hepatic CYP3A activity. Streetman hence investigates the possibility of using a urinary MR following an i.v. midazolam dose in place of collecting multiple blood samples. Twenty subjects completed eight phenotyping visits and detailed information regarding their CYP3A activity, and the effect of fluvoxamine on hepatic CYP3A was measured (page 351). The resulting poor correlations with midazolam total clearance and large degree of variability with the urinary MRs concludes that the suggested use of MR is not an accurate measure of hepatic CYP3A activity (page 354).

Hence, Streetman suggests a MR method including LC/MS/MS to measure CYP3A activity using the specific agent midazolam. Streetman is directed to methods of phenotyping, but for another purpose than selecting patients for a clinical trial, and by other method steps than provided by the claimed invention There is no indication that

hyperpolarized NMR, using a probe compound comprising an active nuclei could be used. There is hence no teaching or suggestion by Streetman to use a fast and simple hyperpolarized NMR spectroscopy method. Further, Streetman reports that the subjects were phenotyped for CYP3A on eight occasions. Comparisons of baseline urinary MR and MR during metabolic inhibition by fluvoxamine were made for each subject (page 351). However, there is no teaching or suggestion by Streetman to select volunteer patients for a clinical trial by phenotyping, grouping said human individuals into groups by their metabolic ratios??? of poor metabolisers and extensive metabolisers; and selecting a group of volunteer patients obtained for use in a clinical trial. Applicant disagrees that Streetman teaches the limitations of steps c) and d). Clearly, the method of Streetman does not point in the direction of selecting volunteer patients with a specific phenotype and using said volunteer patients in a clinical trial. Thus the teaching of Streetman would not have prompted the skilled person faced with the objective of providing a method to identify and select volunteer patients with a specific phenotype to modify or adapt the method of WO2001/096895 for such a purpose.

As neither WO2001/096895 nor Streetman, either alone or in combination, disclose, teach, or suggest the instant invention, Applicants respectfully submit that present invention is patentably distinct thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the amendments and remarks hereinabove, Applicants respectfully submit that the instant application, including amended claims 1, 9-12, and 15-16, is in condition for allowance. Favorable action thereon is respectfully requested.

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Any questions with respect to the foregoing may be directed to the Applicants' undersigned counsel at the telephone number below.

Respectfully submitted,

/Robert F. Chisholm/
Robert F. Chisholm
Reg. No. 39,939

GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6905

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